REMARKS

I. Status of the claims and amendments

After entering this amendment, claims 1-16, 18, 22, and 23 will be pending in this application. Claim 21 has been cancelled without prejudice or disclaimer. Claim 22 has been amended by deleting the following pathological conditions or diseases: atherosclerosis and gastrointestinal tract disorders.

II. Allowable Subject Matter

Applicants acknowledge the Office's indication that claims 1-16, 18 and 23 are free of prior art and are allowed. Office Action at 10.

III. Rejections under 35 U.S.C. § 112, first paragraph

The Office rejected claims 21 and 22 under 35 U.S.C. § 112, first paragraph, alleging that these claims are not enabled. The Office acknowledges that the specification enables the treatment of hypertension, but argues that the specification does not reasonably provide enablement for treating a subject afflicted with a pathological condition or disease susceptible to amelioration by antagonism of the A_{2B} adenosine receptor including asthma, bronchoconstriction, allergic diseases, atherosclerosis, reperfusion injury, myocardial ischemia, retinopathy, inflammation, gastrointestinal tract disorders, cell proliferation disorders, diabetes mellitus, and autoimmune diseases. Office Action at 2.

The Office argues that "claims 21-22, as recited, are reach through claim[s]." *Id.* at 4. According to the Office, "[a] reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through

a scope of invention for which they lack adequate written description and enabling disclosure in the specification." *Id.* The Office concludes that: "claims 21-22 reach through treating any or all pathological conditions and diseases mediated by A_{2B} adenosine receptor in general and thereby they lack adequate written description and enabling disclosure in the specification." *Id.*

Applicants respectfully disagree. Applicants understanding of the PTO's definition of a "reach through" claim is a claim that encompasses subject matter that extends beyond what is disclosed in the application by reciting elements or steps that occur downstream of the subject matter disclosed in the specification. For example, in an application that discloses a specific novel receptor X in a cell, a reach through claim would be one directed to agonists or antagonists of the receptor, where the specification only defines such agonists or antagonists by their functional property of having binding character for the novel receptor X, but discloses no specific examples of such compounds. *See, e.g.*, Example 17 of the Office's Written Description Training Materials dated March 25, 2008.

In contrast, in this case, the instant specification discloses numerous examples of compounds that are selective adenosine A_{2B} receptor antagonists and the rejected claims are directed to subject matter properly supported in the specification. *See, e.g.*, specification at 10-11; 15-33; Examples 1-30. Additionally, as mentioned above, claim 21 has been cancelled without prejudice or disclaimer and claim 22 recites known individual pathological condition or diseases comprising the administration of a compound as claimed in claim 1. Accordingly, the rejected claims are not reach through claims because the recited pathological condition or diseases are known and the

compounds administered are properly described in the specification as compounds of formula I.

The Office argues that "[r]ecent publications expressed that the A_{2B} adenosine receptor inhibition effects are unpredictable and are still exploratory." In support of this statement, the Office cites Sitkovsky et al., *British Journal of Pharmacology*, 153:5457-5464 (2008) ("*Sitkovsky*") and Gao et al., *Expert. Opin. Emerging Drugs* 12(3):479-492, (2007) ("*Gao*"). Office Action at 8. However, *Sitkovsky* is a review of adenosine A_{2A} receptor antagonists and is silent regarding adenosine A_{2B} receptor antagonists, to which the instant invention is directed. For example, the specification indicates that "the compounds of formula (I) are potent inhibitors of the A_{2B} adenosine receptor subtype and very selective over the other adenosine receptor subtypes." Specification at 17, lines 3-5; Table 1 (comparing the effect of the compounds of the invention on the inhibition of A_1, A_{2A}, A_{2B}, and A_3 adenosine receptors.) The Office has not indicated the relevance of the statements regarding adenosine A_{2A} receptor antagonists in *Sitkovsky* on the methods of treatment recited in the claims comprising the administration of inhibitors of the A_{2B} adenosine receptor.

Regarding *Gao*, the Office argues, without citing to any particular passage, that the reference "points out [the] need for further experimentation to establish the usefulness of antagonists of A_{2B} adenosine receptors." *Id.* Applicants respectfully disagree with the Office's interpretation of *Gao*. *Gao* is a review of specific adenosine receptor agonists of all subtypes (A_1, A_{2A}, A_{2B}, and A_3) presently in clinical trials. *Gao* at Abstract (stating: "[t]he present review will mainly cover the agonists that are presently in clinical trials for various conditions and only a brief introduction will be given to major

chemical classes of AR agonists presently under investigation.") *Gao* discusses several specific compounds acting as A_1, A_{2A}, or A_3 adenosine receptor agonists, but only one compound acting as an A_{2B} adenosine receptor agonist, BAY-60-6583. *See*, *Gao* generally, and Table 1 in particular). *Gao* indicates that BAY-60-6583 is being tested for the treatment of cardiac ischemia and reports that "BAY-60-6583 has been shown to be effective in reduction of the infarct size by application after onset of cardiac ischemia in a rabbit infarct model." *Gao* at 488, col. 2, first full ¶. Accordingly, *Gao* clearly supports the notion that A_{2B} adenosine receptor agonists are useful at least in the treatment of cardiac ischemia.

The Office argues that Applicants "have not provided any competent evidence that the instantly disclosed tests are highly predictive for the uses disclosed and embraced by the claim language for the intended host." Office Action at 5. Applicants respectfully remind the Office that enablement needs to be considered, *inter alia*, in light of the state of the art. M.P.E.P. § 2164.01(a). Applicants have shown that the compounds of the invention are inhibitors of the A_{2B} adenosine receptor. Specification at 13 *et seq*; Table 1. As will be shown below, it is well known in the art that inhibitors of the A_{2B} adenosine receptor are useful in the treatment of the diseases recited in the rejected claims, properly enabling one skilled in the art to practice the invention.

Asthma and bronchoconstriction

Numerous journal articles have reported the therapeutic use of A_{2B} adenosine receptor antagonists in the treatment of asthma and bronchoconstriction. For example, R. Polosa, *Eur. Respir. J* 20:488-496 (2002) ("*Polosa*") indicates that "[t]he mechanisms of adenosine-induced bronchoconstriction appear to involve a selective interaction with

activated mast cells with subsequence release of preformed and newly-formed mediators," explaining that "promising adenosine-receptor targets for novel therapeutics of asthma and chronic obstructive pulmonary disease have recently been identified in a number of inflammatory cell types, including mast cells, [among others]." *Polosa* at Abstract. *Polosa* concludes that "[t]he recent characterization of the A_{2B} receptors indicates that the human lung mast cell as one of the most strategic cellular targets." *Id.* *Polosa* and all other references cited in this response are being submitted in an Information Disclosure Statement being filed concurrently with this response.

More recently, S.T. Holgate, *British J. Pharmacology* 145:1009-1015 (2005) ("*Holgate*") reports that "[a]denosine is a powerful bronchoconstrictor of asthmatic, but not normal airways." *Holgate* at Abstract. And, after summarizing experimental results with A_{2B} adenosine receptor antagonists, *Holgate* concludes that "[t]hese data have provided a firm basis for developing adenosine A_{2B} receptor antagonists as a new therapeutic approach to this disease." *Id.* In particular, *Holgate* explains the mechanism of adenosine-induced broncoconstriction (p. 1010, col. 1), how the adenosine receptors mediate the proasthmatic response (p. 1010-1011), and concludes that "[s]ince there is now good evidence to support the involvement of [the] A_{2B} receptor in mast cell activation, promising antagonists for this receptor are being developed, such as IPDX." *Id.* at 1012, col. 1. *Holgate* explains that "[o]ver a span of 20 years, the initial observation of the unique pro-asthmatic effects of inhaled adenosine has evolved to provide the basis for a new asthma therapy." *Id.* at 1012, col. 2.

Also, J. Zablocki et al. *Expert Opin. Ther. Patents* 16(10):1347-1357 (2006) ("*Zablocki*") clearly states that "[e]vidence suggests that A_{2B} AdoRs [A_{2B} adenosine

receptors] may play a role in the following disease states: asthma, in which it mediates inflammatory cytokine release [among other diseases.]" *Zablocki* at 1347; section 1.1. After reviewing some of the available experimental data, *Zablocki* concludes that "the above evidence strongly suggests that adenosine plays a role in asthma, and its effects are, at least in part, mediated through the A_{2B} AdoRs [adenosine receptor.]" *Zablocki* at 1348; col.1.

A more recent article also demonstrates the therapeutic effect of adenosine A_{2B} receptor antagonists in the treatment of asthma and bronchoconstriction. G. Hasko, et al. Nature Reviews 7:759-770 (2008) ("*Hasko*"). *Hasko* indicates that "most compelling are the observations that inhaled adenosine can induce bronchoconstriction in patients suffering from asthma or COPD, but not healthy individuals, and *adenosine receptor blockage [i.e. inhibition] can prevent this bronchoconstrictive response. Hasko* at 765, col. 1 (italics added).

Finally, another recent article, C.N. Wilson, *British J. Pharmacology* 155:475-486 (2008) ("*Wilson*") reports the use of an adenosine A_{2B} receptor antagonist, CVT 6883, in the phase I clinical trial for the treatment of asthma, which clearly demonstrates the use of A_{2B} receptor antagonists for this indication. *See, e.g., Wilson* at Table 1.

Therefore, in view of the experimental evidence cited above, it is clear that adenosine A_{2B} receptor antagonists are effective therapeutic agents for the treatment of asthma and bronchoconstriction.

Hypertension

The Office already acknowledged that the specification enables the treatment of hypertension. Office Action at 2 (indicating that "the specification while enabling for treating hypertension, does not [enable the treatment of the rest of the diseases.]"

Inflammation

The Office argues that "[f]or a compound or genus to be effective against inflammation generally is contrary to medical science" because "[t]here is no common mechanism by which all, or even most, inflammations arise." Office Action at 5. The Office further argues that "treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no 'magic bullet' against inflammation generally." In response, Applicants point out that the type of inflammation recited in claim 22 is limited to that inflammation that is associated with the adenosine A_{2B} receptor and that is "susceptible to amelioration by antagonism of the A_{2B} adenosine receptor."

Applicants also point out that there are various journal articles that conclusively state that antagonism of the A_{2B} adenosine receptor leads to a reduction of inflammation. For example, *Hasko* states that "A_{2B} receptor activation has broad pro-inflammatory actions y stimulating the pro-inflammatory functions of a variety of cell types [such as fibroblasts, smooth-muscle cells, lung epithelial cells, mast cells, endothelial cells, and machrophages]." *Hasko* at Fig. 4. Among the cytokines and inflammatory factors produced by these cells are IL-3, IL-4, IL-6, IL-8, IL-13, VEGF, and histamine. *Id.* *Hasko* explains that there is "substantial evidence documenting the pro-inflammatory effects of selective A_{2B} receptor activation in human and rodent cellular

systems" and also showing "*the utility of A_{2B} receptor antagonism* in preventing the disease progression in rodent animal models." *Hasko* at 765, col. 2 (italics added).

Wilson also reports that the selective adenosine A_{2B} receptor antagonist CVT 6883, which is being used in phase I clinical trials, acts as an anti-inflammatory in asthmatics. *Wilson* at Table 1; see also *Hasko* at Table 1.

Allergic and autoimmune diseases

To the extent that allergic and autoimmune diseases are mediated by the activation of the A_{2B} adenosine receptor and the subsequent regulation of immune and inflammatory systems, which was demostrated in the section above for inflammation, administration of adenosine A_{2B} receptor antagonists should also lead to the treatment of allergic and autoimmune diseases.

Reperfusion injury and myocardial ischemia

WO 03/105666 demonstrates that adenosine A_{2B} receptor antagonists can be used in the treatment of reperfusion injury and myocardial ischemia. For example, the inventors of WO 03/105666 state that they "discover[ed] that A_{2B} adenosine receptor antagonists are capable of preventing, limiting, or treating ischemia reperfusion injury." WO 03/105666 at 4, lines 27-31.

Also, *Gao*, cited by the Office, indicates that "[o]ne of the potent and selective non-adenosine A_{2B}AR [A_{2B} adenosine receptor] antagonists, has been shown to be effective in reduction of the infarct size by application after the onset of cardiac ischemia in a rabbit infarct model." *Gao* at 488, col. 2, first full ¶. Accordingly, *Gao* clearly supports the notion that A_{2B} adenosine receptor agonists are useful in the treatment of cardiac ischemia.

Cell proliferation disorders and retinopathy

J.N. Peart et al., *Pharmacology & therapeutics* 114:208-221 (2007) ("*Peart*") states that "the A_{2B}AR [A_{2B} adenosine receptor] is known to activate angiogenic factors and trigger coronary endothelial growth." *Peart* at 212, section 3.2, col. 1. *Peart* concludes that "this [A_{2B}] subtype may play a role in modulation of vascular growth and tissue remodeling." *Id.* More explicitly, *Zablocki* states that "[e]vidence suggests that A_{2B} AdoRs [A_{2B} adenosine receptors] may play a role in the following disease states: . . . diabetic retinopathy and cancer, in which it mediates angiogenesis [among other diseases.]" *Zablocki* at 1347; section 1.1.

Accordingly, the state of the art clearly indicates the benefits of adenosine A_{2B} receptor antagonists in the treatment of diabetic retinopathy and cancer when these diseases are mediated by angiogenesis.

Diabetes mellitus

Zablocki also states that "[e]vidence suggests that A_{2B} AdoRs [adenosine receptors] may play a role in the following disease states: . . . diabetes, in which it mediates gluconeogenesis [among other diseases.]" *Zablocki* at 1347; section 1.1. *Zablocki* reports that "[a] non-selective high affinity A_{2B} AdoR antagonist was shown to lower plasma glucose following oral dosing (10 and 30 mg/Kg bodyweight) in a mouse model of non-insulin dependent diabetes mellitus." *Zablocki* at 1348, col. 1. The same information regarding use of adenosine A_{2B} receptor antagonists in the treatment of diabetes is reported in K. Jacobson et al. *Nature Reviews* 5:247-264 (2006) at 259, col. 2.

Accordingly, the state of the art is such that the pathological conditions or diseases mediated by the adenosine A_{2B} receptor that are recited in claim 22 can be treated with adenosine A_{2B} receptor antagonists. Accordingly, claim 22 is enabled and Applicants respectfully request that this rejection be withdrawn.

Applicants reserve the right to file a continuation application directed to the subject matter of cancelled claim 21 and the pathological conditions and diseases deleted from claim 22.

IV. Conclusions

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees not paid at the time of filing this document to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: January 7, 2009